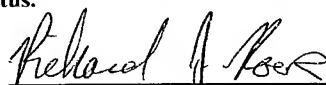


U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE FORM PTO-1390 (Modified) (REV 11-2000)		ATTORNEY'S DOCKET NUMBER <b>71745/56925</b>
<b>TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371</b>		U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR <b>10/049488</b>
INTERNATIONAL APPLICATION NO <b>PCT/GB00/03142</b>	INTERNATIONAL FILING DATE <b>15/08/2000 (15 AUGUST 2000)</b>	PRIORITY DATE CLAIMED <b>17/08/1999 (17 AUGUST 1999)</b>
TITLE OF INVENTION <b>SAMPLING/DISPENSING DEVICE WITH PLUNGER AND HOUSING SET ONTO PLUNGER</b>		
APPLICANT(S) FOR DO/EO/US <b>RICHARD KELBY EDWARDS, JOHN CASSELLS, NICHOLAS IAN MOUNTENEY, AND GERALD AVISON</b>		
<p>Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:</p> <ol style="list-style-type: none"> <li>1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li>2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li>3. <input type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.</li> <li>4. <input type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31).</li> <li>5. <input type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371 (c) (2)) <ul style="list-style-type: none"> <li>a. <input type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau).</li> <li>b. <input type="checkbox"/> has been communicated by the International Bureau.</li> <li>c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</li> </ul> </li> <li>6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)). <ul style="list-style-type: none"> <li>a. <input type="checkbox"/> is attached hereto.</li> <li>b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4).</li> </ul> </li> <li>7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3)) <ul style="list-style-type: none"> <li>a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau).</li> <li>b. <input type="checkbox"/> have been communicated by the International Bureau.</li> <li>c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</li> <li>d. <input type="checkbox"/> have not been made and will not be made.</li> </ul> </li> <li>8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</li> <li>9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).</li> <li>10. <input type="checkbox"/> An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).</li> <li>11. <input checked="" type="checkbox"/> A copy of the International Preliminary Examination Report (PCT/IPEA/409).</li> <li>12. <input checked="" type="checkbox"/> A copy of the International Search Report (PCT/ISA/210).</li> </ol> <p><b>Items 13 to 20 below concern document(s) or information included:</b></p> <ol style="list-style-type: none"> <li>13. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</li> <li>14. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</li> <li>15. <input checked="" type="checkbox"/> A <b>FIRST</b> preliminary amendment.</li> <li>16. <input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment.</li> <li>17. <input type="checkbox"/> A substitute specification.</li> <li>18. <input type="checkbox"/> A change of power of attorney and/or address letter.</li> <li>19. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.</li> <li>20. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4).</li> <li>21. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).</li> <li>22. <input checked="" type="checkbox"/> Certificate of Mailing by Express Mail</li> <li>23. <input checked="" type="checkbox"/> Other items or information: <b>PCT/IPEA/416; PCT/IB/304; PCT/IB/308; PCT/IPEA/401; PCT/IPEA/402; PCT/IPEA/408; PCT/RO/101; A COPY OF PUBLISHED INT'L APPLICATION NO. WO 01/12329 A1; DUPLICATE COPY OF PAGE 2 OF THIS TRANSMITTAL LETTER; A CHECK IN THE AMOUNT OF \$445.00 (CK NO. 706886) REPRESENTING THE FILING FEE; AND RETURN POSTCARD.</b></li> </ol>		

U.S. APPLICATION NO (IF KNOWN, SEE 37 CFR <b>10/049488</b>	INTERNATIONAL APPLICATION NO <b>PCT/GB00/03142</b>	ATTORNEY'S DOCKET NUMBER <b>71745/56925</b>	
24. The following fees are submitted:	<b>CALCULATIONS PTO USE ONLY</b>		
<b>BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :</b>			
<input type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... <b>\$1040.00</b> <input checked="" type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... <b>\$890.00</b> <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... <b>\$740.00</b> <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... <b>\$710.00</b> <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) ..... <b>\$100.00</b>			
<b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>	<b>\$890.00</b>		
Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		<b>\$0.00</b>	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE
Total claims	14 - 20 =	0	x \$18.00 <b>\$0.00</b>
Independent claims	2 - 3 =	0	x \$84.00 <b>\$0.00</b>
Multiple Dependent Claims (check if applicable).		<input type="checkbox"/> <b>\$0.00</b>	
<b>TOTAL OF ABOVE CALCULATIONS =</b>	<b>\$890.00</b>		
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.		<b>\$445.00</b>	
<b>SUBTOTAL =</b>	<b>\$445.00</b>		
Processing fee of <b>\$130.00</b> for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).		<input type="checkbox"/> + <b>\$0.00</b>	
<b>TOTAL NATIONAL FEE =</b>	<b>\$445.00</b>		
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).		<input type="checkbox"/> <b>\$0.00</b>	
<b>TOTAL FEES ENCLOSED =</b>	<b>\$445.00</b>		
		Amount to be: refunded	\$
		charged	\$
a. <input checked="" type="checkbox"/> A check in the amount of <b>\$445.00</b> to cover the above fees is enclosed.			
b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.			
c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <b>04-1105</b> A duplicate copy of this sheet is enclosed.			
d. <input type="checkbox"/> Fees are to be charged to a credit card. <b>WARNING: Information on this form may become public. Credit card information should not be included on this form.</b> Provide credit card information and authorization on PTO-2038.			
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.			
SEND ALL CORRESPONDENCE TO:			
<b>DAVID G. CONLIN, ESQ. (REG. NO.: 27,026)</b> <b>DBRC, INTELLECTUAL PROPERTY PRACTICE GROUP OF</b> <b>EDWARDS &amp; ANGELL, LLP</b> <b>P.O. BOX 9169</b> <b>BOSTON, MASSACHUSETTS 02209</b> <b>TEL.: 617-439-4444</b> <b>FAX: 617-439-4170</b> <b>DGC@EALAW.COM</b>			
 <b>SIGNATURE</b> <b>RICHARD J. ROOS, ESQ.</b> <hr/> <b>NAME</b> <b>45,053</b> <hr/> <b>REGISTRATION NUMBER</b> <b>FEBRUARY 12, 2002</b> <hr/> <b>DATE</b>			

10/049488  
JC11 Rec'd PCT/PTO 12 FEB 2002  
Customer No.: 21874

Attorney Docket No. 56925 (71745)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**APPLICANTS:** Richard Kelby Edwards et al.      **EXAMINER:** Not Yet Known

**U.S.S.N.:** Not Yet Assigned  
(National Phase Application based on PCT/GB00/03142)

**FILED:** HEREWITH      **ART UNIT:** Not Yet Known

**TITLE:** SAMPLING/DISPENSING DEVICE WITH PLUNGER AND  
HOUSING SET ONTO PLUNGER

\*\*\*\*\*  
**CERTIFICATE OF MAILING**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: **BOX PCT**, Commissioner for Patents, Washington, D.C. 20231 on February 12, 2002.

By: 

Donna R. Davis

\*\*\*\*\*  
**BOX PCT**  
Commissioner for Patents  
Washington, D.C. 20231

**PRELIMINARY AMENDMENT TO ACCOMPANY NATIONAL STAGE FILING**

Sir:

Prior to examining the enclosed application, please enter the following amendments to the above-referenced National Stage PCT application.

**In the Claims**

Please cancel claims 1-8 without prejudice; and

Please enter the following new claims:

USSN: Not Yet Assigned

(U.S. National Phase Application based on PCT/GB00/03142)

Richard Kelby Edwards et al.

Page 2

9. (New) A method of making a positive displacement type substance sampling and dispensing device, comprising molding and setting a second material around a central plunger having an outer surface and being formed of a first drawn material, such that the second material forms a barrel corresponding to the outer surface of the plunger.

10 (New) A method according to claim 9, wherein the first drawn material is selected from the group consisting of drawn wire and extruded metal.

11. (New) A method according to claim 9, wherein the first drawn material is selected from the group consisting of a metal, a ceramic, and a plastic material.

12. (New) A method according to claim 9, wherein the second material is a plastic material.

13. (New) A method according to claim 9, wherein the first drawn material is actively cooled during the molding step.

14. (New) A method according to claim 9, wherein each of the first drawn material and the second material has a thermal conductivity and a specific heat capacity, and wherein a relationship of the thermal conductivities and specific heat capacities of the first drawn material and the second material is selected from the group consisting of:

(a) the thermal conductivity of the first drawn material is greater than the thermal conductivity of the second material,

USSN: Not Yet Assigned

(U.S. National Phase Application based on PCT/GB00/03142)

Richard Kelby Edwards et al.

Page 3

(b) the specific heat capacity of the first drawn material is greater than the specific heat capacity of the second material, and

(c) the thermal conductivity of the first drawn material is greater than the thermal conductivity of the second material, and the specific heat capacity of the first drawn material is greater than the specific heat capacity of the second material.

15. (New) A method according to claim 9, wherein the molding step comprises performing one of the steps from the group consisting of injection molding, welding, coextrusion casting and dip coating.

16. (New) A method according to claim 9, wherein the barrel, as formed, has a uniform cylindrical shape.

17. (New) A positive displacement type substance sampling and dispensing device made in accordance with the method of claim 9.

18. (New) A device according to claim 17, wherein the device is attached to a flexible strip in a manner to allow for attachment of a plurality of additional devices.

19. (New) A device according to claim 18, wherein the strip includes a plurality of sprocket holes defined therein to drive and align any attached device.

USSN: Not Yet Assigned

(U.S. National Phase Application based on PCT/GB00/03142)  
Richard Kelby Edwards et al.

Page 4

20. (New) A device according to claim 17, wherein the molded and set first drawn material forms a housing having an end at which a removable frangible tip is provided.

21. (New) A device according to claim 17, wherein the device is formed to include a heat sealable tip.

22. A device according to claim 17, wherein the device includes first and second plungers arranged on different axes to allow the first plunger and second plunger to slide within different regions of the molded and set second material, and wherein the different regions are joined at a central common core adjacent to an aperture.

USSN: Not Yet Assigned

(U.S. National Phase Application based on PCT/GB00/03142)  
Richard Kelby Edwards et al.

Page 5

**R E M A R K S**

This preliminary amendment is being filed concurrently with the United States National Stage PCT filing of International Application No. PCT/GB00/03142.

Applicants respectfully request entry of this amendment prior to consideration of this National Stage application.

The amendments included herein are intended to update the International Application such that it reflects amendments that were formally introduced in Applicants' November 2, 2001 amendment and response to a Written Opinion that was received in connection with the International Phase of this International Application.

The claims (1-14) that were introduced in the November 2, 2001 amendment are substantially identical to claims 9-22 set forth above, except that the latter have been amended to be more in harmony with U.S. patent practice.

Although Applicants have canceled claims 1-8 of the International Application herein, they respectfully reserve the right to prosecute identical or similar claims in this, or a related application.

Applicants submit that this National Phase application is in condition for allowance, and, accordingly, early consideration and allowance of the application is respectfully requested.

USSN: Not Yet Assigned

(U.S. National Phase Application based on PCT/GB00/03142)  
Richard Kelby Edwards et al.

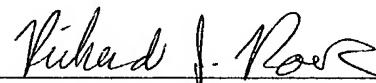
Page 6

If the undersigned can be of any assistance in advancing the prosecution of this case, the Examiner is invited to contact him through the information given below.

Respectfully submitted,

Date: February 12, 2002

By:



Richard J. Roos, Reg. No. 45,053  
Dike, Bronstein, Roberts & Cushman  
Intellectual Property Group  
EDWARDS & ANGELL, LLP  
P.O. Box 9169  
Boston, MA 02209  
Tel: 617-439-4444  
Fax: 617-439-4170  
Email [rroos@ealaw.com](mailto:rroos@ealaw.com)

BOS2\_190568 1

12 FEB 2002

10 / 049488

WO 01/12329

PCT/GB00/03142

## SAMPLING/DISPENSING DEVICE WITH PLUNGER AND HOUSING SET ONTO PLUNGER

This invention relates to a positive displacement type substance sampler/dispenser.

5 One example of such a dispenser is a plunger-type pipette. Such a pipette is in common usage. It generally comprises an outer cylindrical housing having a central bore in which a plunger sits. The plunger can be slid within the bore to either dispense a substance, such as a  
10 fluid or particulate matter, from an orifice in one end of the housing or, if slid in the opposite direction, to draw a fluid or particulate matter into the housing. Such a dispenser has particular benefits in that it can draw up and dispense substances with a high degree of accuracy.  
15 Devices in current use do, however, have problems associated with them.

Firstly, it is extremely difficult to produce a device which has a parallel housing bore, meaning that the relationship between the volume of the substance drawn up  
20 or dispensed is not linearly relative to the amount of displacement of the plunger. This is particularly true for low volume devices. Furthermore, it is extremely difficult to produce a bore to a level of accuracy which ensures that there is a tight fit between the plunger and the bore wall,  
25 meaning that fluid can pass around the edges of the plunger, leading to a reduction in sampling/dispensing accuracy, and leading to a risk of leakage.

The piston is typically slightly oversize for the bore such that it forms an interference fit for sealing. To  
30 accommodate this, and to allow for the draft angle on the bore, either the piston or the bore may be made from a compliant material. Examples are medical syringes having rigid polystyrene bores and rubber piston ends, or stiff polypropylene pistons with a compliant thin-walled bore.  
35 An alternative sealing arrangement is to provide a lip seal at the end of the piston. These constructions have many disadvantages. In general, compliant materials cannot be

used where chemical resistance is required; it becomes increasingly difficult to injection mould bores as the diameter is reduced such that devices capable of accurate dispensing over the nanolitre range are not possible; the 5 need for a draft angle and conventional moulding techniques limits the practical length and thus the dynamic range of the pipette; and the manufacture of pistons with lip seals becomes increasingly difficult as the diameter is reduced below 1 mm.

10 Thus, present methods of construction are not suited to long bore, high accuracy, low cost and sub-microlitre devices.

15 Other problems associated with such devices includes the fact that they are difficult to handle automatically, their manufacture is costly, and it is often difficult to alter the materials from which the plunger and housing are made without changing moulding tooling for both components.

20 According to a first aspect of the present invention, there is provided a positive displacement type substance sampling and dispensing device comprising:

a central plunger formed from a first material; and  
25 a plunger housing formed from a second material, the housing being formed by moulding and setting the second material on to the surface of the plunger so that the plunger can slide in the housing to draw a substance into it.

The first material may be metal, plastic, ceramic or other suitable material. The plunger may be formed from drawn wire or extruded material to ensure that it has a 30 uniform diameter. The housing may be moulded onto the plunger by injection moulding, welding, coextrusion, casting, dip coating etc.

35 The materials may be selected such that, preferably, the material of the piston is stiffer and/or has a lower thermal expansion coefficient than the material of the bore. If heat is applied during manufacture, such as using molten plastic to form a bore around a metal wire, the bore

will progressively tighten around the piston as the device cools down, thus forming a better seal. If the piston can be maintained at a lower temperature than the material of the bore during forming, it is possible to get further 5 improved sealing because the piston will have expanded even less with respect to the bore. The piston may be actively cooled, or may exploit a higher thermal conductivity or specific heat capacity property than the material of the bore.

10 During its manufacture, the device may be attached or incorporated into a flexible strip or other backing to which further devices are attached for ease of automated handling.

15 The flexible strip may have sprocket holes to drive and align the pipettes.

Alternatively, the devices may be manufactured as single discrete pipettes. The pipettes are operated by gripping both the plunger housing and plunger of the pipette and moving the plunger within the bore in the same 20 way as a conventional positive displacement pipette. This operation may be performed by a manual or automatic device. The devices may be used singly or in multiples with or without a backing strip.

25 The material of the strip may itself form part or all of the housing of the device.

The housing may be formed so that at one end of the device there is provided a frangible tip which can be removed before use to prevent contamination of the device prior to use.

30 Alternatively, the device may be formed so that it has a heat sealable tip, allowing for the loading of the apparatus with a substance, the substance being sealed in place by sealing of the tip.

35 The device may also be incorporated into fluidic devices such as "chip-based" analytical devices, chemical synthesizers and sensors to provide a means of forming capillaries, valves and pumps, for example.

The device may have plural plungers arranged on different axes and each sliding within a different region of the housing, the different regions of the housing being joined at a central common core adjacent to an aperture.

5 By forming the housing around the plunger the cost of manufacture of the device is reduced considerably. Furthermore, such a device has a highly effective seal between the plunger and the housing, and can also be ensured of having a uniform cylindrical wall, even if it is  
10 arranged for the dispensing/sampling of very small samples.

15 The device may be formed by moulding the bore round a drawn wire such that it produces a pipette with a perfectly cylindrical bore throughout. In use, the drawn wire may be projected beyond the tip of the device to pierce the seal of a storage vessel or to act as an ultrasonic probe or electrode for automatic level sensing. A second conductor may be provided parallel to the piston to act as a counter electrode.

20 The bore may be formed around a piston which has had its tip ground to a shaped point. This provides for an aperture that is a smaller diameter than the bore at the tip of the device, which is important for retaining liquid in larger bore devices.

25 One example of the present invention will now be described with reference to the accompanying drawings, in which:

Figure 1 is a schematic cross-sectional view of a known sampling/dispensing device;

30 Figure 2 is a side cross-sectional view of a device according to the present invention during a first stage of manufacture;

Figure 3 is a side cross-sectional view of a device according to the present invention after manufacture;

35 Figure 4 is a side view of a number of the devices according to the present invention attached to a flexible strip for ease of handling;

Figure 5 is a side cross-sectional view of a further example of the present invention;

Figure 6 is a perspective view of a number of the devices according to the present invention attached to a  
5 flexible strip;

Figure 7 shows the results of volumetric accuracy trials performed with one example of the present invention; and

10 Figure 8 shows photo-micrographs of a cross section of a pipette made by the process of example 1.

Referring to Figure 1, a prior art positive displacement-type pipette has an outer housing 1 which has a plunger 2 slidably retained therein. The plunger 2 can be moved to draw a sample into the housing 1 or expel a  
15 sample from the housing 1 via an aperture 3. The plunger 2 has a head 4 formed from relatively hard material and which is resilient enough to compensate for a variation in housing diameter with respect to the position of the plunger 2 within the housing. The disadvantages of this.  
20 device, in terms of difficulty of manufacture, inaccuracies and leakage problems, are discussed above.

Figure 2 is a side cross-sectional view of a device 10 in accordance with the present invention during manufacture. The device 10 has a central plunger 12, in  
25 this example formed from drawn metal, and an outer housing 11. The outer housing 11 is moulded onto the plunger 12. If a thermoplastic (for example, polyethylene or polypropylene) is used to form the outer housing the plunger should be formed from a material with a higher  
30 melting point and preferably lower thermal expansion coefficient than the housing. The plunger, may for example, be made of metal, glass, plastic or ceramic. The housing may also be formed from a thermoset material (for example, silicone rubber or polyurethane resin) or a  
35 thermoplastic dissolved in solvent (for example polycarbonate or polyvinylchloride in solvent) in which case the plunger material need not have a higher melting

point than the housing. It is preferable to use a thermoset that shrinks on curing.

The housing 11 may be formed by injection moulding, extrusion, or any other well known casting, ultrasonic, 5 welding, dip-coating, co-extrusion, powder coating, thermoforming, spraying forming technique. Once the housing 11 has cooled and set the device can be trimmed to length. In use the plunger 12 can be drawn into the housing, leaving an aperture 13 and an inner core 14 into 10 which a sample can be drawn during use. The inner core 14 is a uniform cylinder as it corresponds to the outer surface of the plunger 12. Furthermore, it is in extremely close engagement with the plunger 12 because of the moulding techniques employed.

15 Figure 4 shows how the device 10 of the present invention may be attached to one or more flexible strips 15 for ease of handling. In particular, such an arrangement is handled very easily by automated machinery. In practice, because of the extremely low cost nature of the 20 manufacture of the device 10, it can be treated as a disposable item in use.

Variations of the construction of the device 10 are 25 possible. Firstly, the housing 11 may be formed over the end of the plunger 12 and arranged so that, in use, it has a frangible region which can be snapped off just prior to device use to prevent contamination of the plunger end. Furthermore, the device 10 may be provided with a heat sealable region adjacent to the aperture 13, so that a substance can be placed in the core 14 of the device 10 and 30 sealed therein. This provides a sealed device that, once the end is cropped off, can meter and deliver the contents without loss.

A further alternative arrangement is shown in Figure 5. In this arrangement, plural plungers 12 have a outer 35 housing 11 formed thereon. All of the plungers 12 are able to access a common core 14 and tip 13. By withdrawing the pistons, capillary paths are created in the device. Liquid

can be drawn up and moved through the system very precisely by moving the pistons. Where capillaries intersect the pistons may be operated as active valves to stop or regulate flow. A viewing window (not shown) may be incorporated into devices to allow the contents to be analysed by a detector. Such an arrangement provides for an extremely cost effective multiple sample withdrawal and dispensing arrangement that still has an high degree of sampling/dispensing accuracy and extremely low leakage.

This type of arrangement is not limited to the simple example shown. A multitude of pumps, capillaries and valves may be incorporated into three dimensional fluidic devices such as "chip-based" analytical devices, chemical synthesisers and sensors using the method of the invention.

There are now described three examples which have proved to be particularly advantageous.

#### Example 1

Figure 4 shows a device constructed according to the present invention. Hard drawn and polished stainless steel wire (British Standard 2056 302S26) of 0.40 mm diameter is inserted into high density polyethylene (HDPE) tubing of 0.43 mm ID and 0.66 mm OD. The tubing length is chosen as 23 mm and the wire length as 30 mm, to leave 7 mm of wire protruding. This tubing is placed across a tape 30 mm wide, made of 0.175 mm polypropylene film. The tubing with wire insert is then welded onto the backing tape using a hemi-cylindrical ultrasonic weld horn along the length of the plastic tube. This applies pressure and melts the plastic tube such that the tube material flows around the wire. This eliminates the 0.03 mm clearance between the wire and the tubing stock. A pipette is thus formed and is simultaneously welded to the backing film in one operation. Multiple pipettes can be formed in a continuous step-and-repeat process.

The tape can then be die-cut to crop the tubing and wire to form the pipette shapes and sprocket holes 16 in one operation.

The backing tape is cut to provide slender pipettes.

Pipettes may be cut from the backing tape and used singly, or may be retained on the backing tape and used in multiples. The backing tape pitch was chosen to be a 5 multiple of 2.25 mm (in this case 4.5 mm) to match the pitch of standard 96, 384 and 1536-well microtitre plates.

An aspirate/dispense head can be constructed to grip the backing tape or barrel and pistons independently, and to drive the pistons up and down under user or automatic 10 control to achieve metering (not shown). Volumetric accuracy trials were performed with the prototype device by aspirating 100, 200, 300, 400 and 500 nl samples of writing inks and dispensing them into dry receptacles with tipping off. The results were determined gravimetrically and are 15 shown in figure 7. This shows that even non-optimised devices following this invention are capable of accurately aspirating and dispensing samples as small as 100 nl.

Trials with prototype devices of the above construction were carried out to test their performance as 20 storage devices. 100 nl of air was drawn into each device, followed by 100 nl of water and finally another 100 nl of air. Devices were tested with open and sealed ends. The ends were sealed by dipping into hot wax, hot melt glue or by heat welding them closed. Samples were stored for 30 25 days at room temperature, -20°C and -74°C. The open-ended pipettes lost weight rapidly at room temperature, losing all the samples in six hours. All other samples showed no detectable weight loss over the test.

The advantage of this approach for storage is that all 30 of the material stored can be recovered and the storage device can also be used to meter and dispense the stored sample.

Figure 8 shows a photomicrograph of a cross-section of 35 a pipette made by the process of example 1. The 0.3 mm diameter wire has been withdrawn. The out-of-round distortion was caused by the blade used to cut the section.

On re-inserting the wire plunger the device assumes a circular cross-section.

A further device was made by the method above, but using polyethylene-coated PET film for the backing tape.

5 The PET layer provides a stiffer backing tape more suited for mechanical feed.

#### Example 2

A device according to present invention was constructed by insert moulding 0.5 mm diameter stainless 10 steel wire into mould-making grade silicone rubber. A mould was made from three 3 mm thick aluminium sheets sandwiched between two 1 mm thick sheets of glass such that a void 100 mm long, 20 mm high and 3 mm thick was formed. The assembly was held together with spring clips and the 15 top of this void was open to allow filling with resin. An array of stainless steel wires was suspended above the mould with the ends of the wires protruding to the bottom of the mould. Silicone resin was poured into the mould and allowed to cure. Once set, the clips were released and the 20 glass sides taken off the mould to allow the device to be removed. After shaping the pipettes with a knife the wires were cropped to length to form pistons. Operation of the resulting prototype demonstrated suitable function as a pipette.

25        Example 3

A device according to the present invention was constructed by sandwiching stainless steel entomology pins (0.38 mm diameter, 38 mm long, size 00) between polypropylene tapes 0.2 mm thick by 30 mm wide 300 mm long. 30 The pins were laid across one plastics material and the second plastic tape was over-laid to form a sandwich. The plastic sheets were joined together and heat-welded around and along the length of each individual pin between two hemi-cylindrical heated formers. This caused the 35 polypropylene to flow around the pins, thus forming a barrel around each piston. The tape was then cut to form an array of pipettes following the method of Example 1.

**Example 4**

A stiff stainless steel wire of 0.4 mm diameter (EN304, BS1554 or similar) was coated with an extruded polyethylene (PE) sheath to give an overall diameter of 5 0.80 mm.

Conventional equipment for making insulated electrical wire was used to make the coated wire, but with the process and settings revised to accommodate the wire hardness and the polyethylene coating material. This coated wire was 10 straightened and cut into pipettes of 20 mm length. The coating was stripped off from one end of each pipette to provide a shank 4 mm long. This shank may be gripped to move the plunger in the barrel of the pipette. Conventional electrical wire can be used to make devices of 15 the present invention, but performance is poor because the wire is not stiff enough to allow operation against a tight seal, copper is not desirable as a material in contact with chemical and biological samples, and the PVC coating does not have the desirable properties. The pipette thus formed 20 can be used singly, or preferably is joined transversely to a backing strip.

A backing strip was formed by cutting polyester/Surlyn/EVA film (thickness 125 $\mu\text{m}$  overall) to form a carrier tape with tabs along one edge and sprocket holes 25 for transport (figure 4). Pipettes were ultrasonically welded to this carrier tape at 4.5 mm intervals. Strips of pipettes or individual pipettes can be cut off this carrier tape for subsequent use.

CLAIMS

1. A method of making a positive displacement type substance sampling and dispensing device, comprising moulding and setting a second material around a central plunger formed of a first drawn material, such that the second material forms a barrel corresponding to the outer surface of the plunger.
2. A method according to claim 1, wherein the first drawn material is drawn wire or extruded metal.
- 10 3. A method according to claim 1, wherein the first drawn material is one of metal, plastic and ceramic.
4. A method according to any one of the preceding claims, wherein the second material is plastics material.
- 15 5. A method according to any one of the preceding claims, wherein the first drawn material is actively cooled during moulding.
- 20 6. A method according to any one of the preceding claims, wherein the first drawn material has a higher thermal conductivity and/or specific heat capacity than the second material.
7. A method according to any one of the preceding claims, wherein the step of moulding comprises one of injection moulding, welding, coextrusion casting and dip coating.
- 25 8. A method according to any preceding claim, wherein the barrel is formed to be a uniform cylinder.
- 30 9. A positive displacement type substance sampling and dispensing device made in accordance with the method of any preceding claim.

## 12

10. A device according to claim 9, attached to a flexible strip, to which further devices are attached in use.

11. A device according to claim 10, wherein the strip has sprocket holes to  
5 drive and align the devices attached thereto.

12. A device according to any of claims 9 to 11, wherein the moulded and set  
first material forms a housing, which is provided, at one end thereof, with a  
frangible tip which can be removed before use.

10

13. A device according to any of claims 9 to 11, wherein the device is formed  
so that it has a heat sealable tip.

14. A device according to any of claims 9 to 13 comprising plural plungers  
15 arranged on different axes and each sliding within a different region of the  
moulded and set second material, the different regions being joined at a central  
common core adjacent to an aperture.

AMENDED SHEET

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
22 February 2001 (22.02.2001)

PCT

(10) International Publication Number  
**WO 01/12329 A1**

(51) International Patent Classification<sup>7</sup>: **B01L 3/02 //** AVISON, Gerald [GB/GB]; 59 Victoria Park, Cambridge A61M 5/31 CB4 3EJ (GB).

(21) International Application Number: **PCT/GB00/03142**

(74) Agent: **GILL JENNINGS & EVERY**; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).

(22) International Filing Date: 15 August 2000 (15.08.2000)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
99306463.3 17 August 1999 (17.08.1999) EP

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

Published:

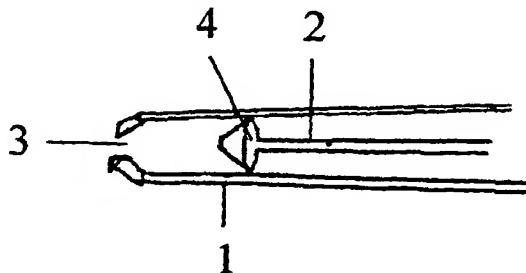
(75) Inventors/Applicants (*for US only*): **EDWARDS, Richard, Kelby** [GB/GB]; 7 Leys Walk, Hauxton, Cambridge CB2 5HZ (GB). **CASSELLS, John** [GB/GB]; The Technology Partnership plc, Melbourn Science Park, Cambridge Road, Melbourn, Royston, Herts SG8 6EE (GB). **MOUNTENEY, Nicholas, Ian** [GB/GB]; 30A Owl Way, Hartford, Huntingdon, Cambridgeshire (GB).

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SAMPLING/DISPENSING DEVICE WITH PLUNGER AND HOUSING SET ONTO PLUNGER

WO 01/12329 A1



(57) Abstract: A positive displacement type substance sampling and dispensing device comprises a central plunger formed from a first material. A plunger housing is formed from a second material having a melting point lower than the first material, or otherwise being capable of being moulded around the first material, the housing being formed by moulding and setting the second material on to the surface of the plunger so that the plunger can slide in the housing to draw a substance into it.

1/6

Figure 1

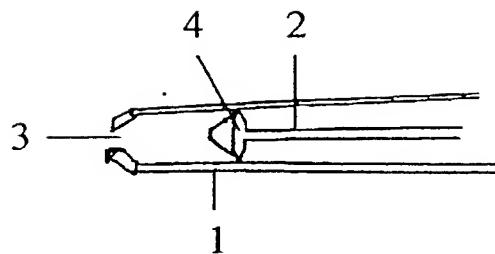


Figure 2

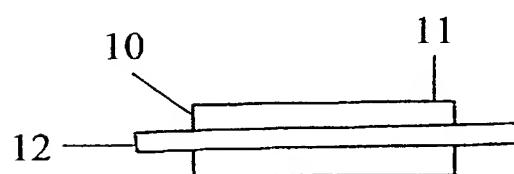
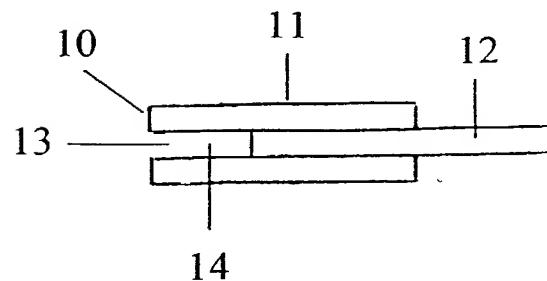
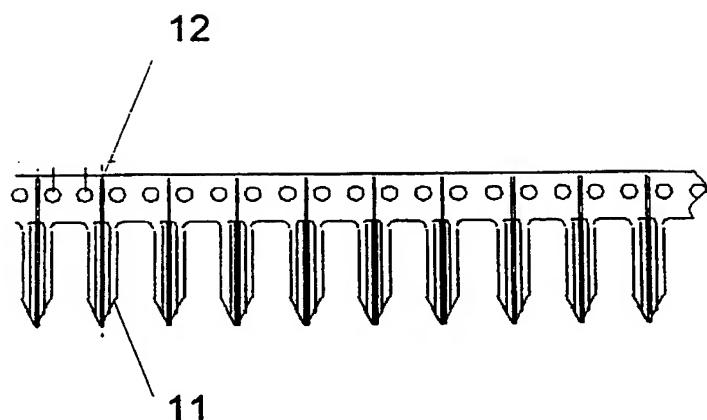


Figure 3



**Figure  
4**



3/6

Figure 5

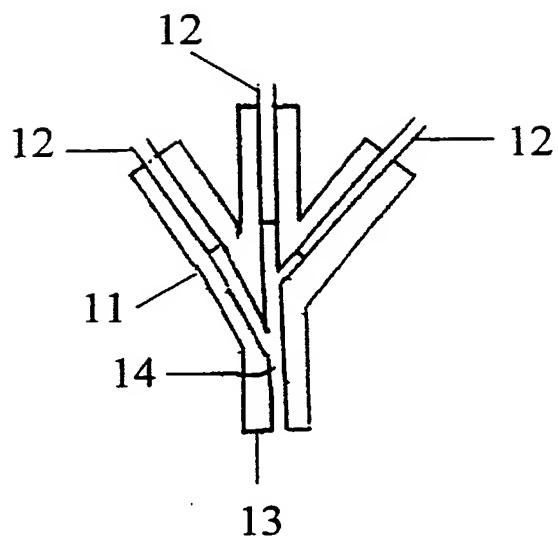


Figure 6

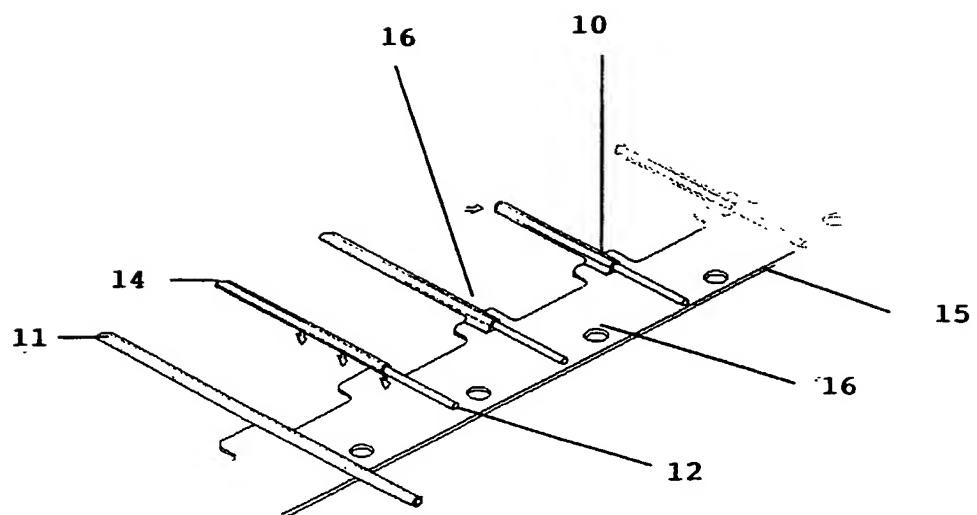
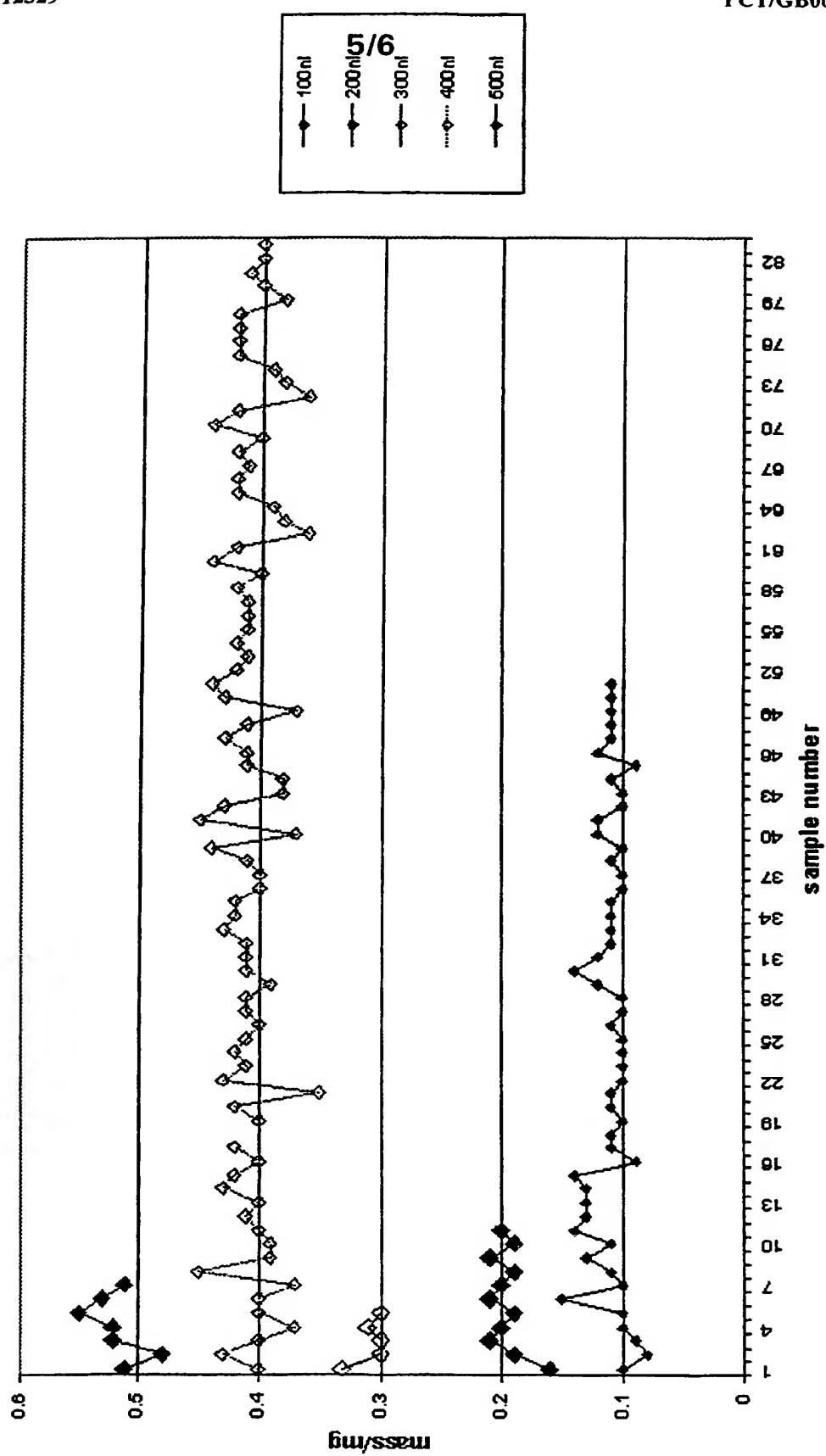


Figure 7 - Volumetric data for prototype pipettes



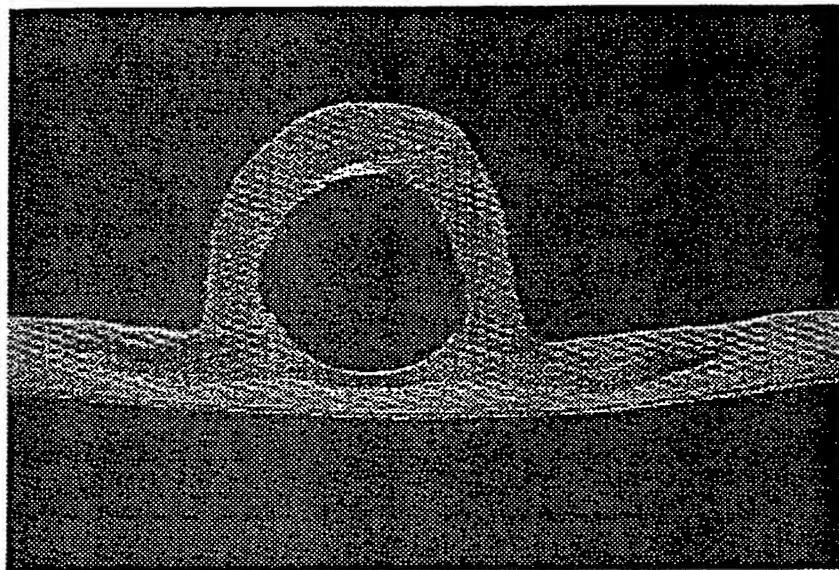
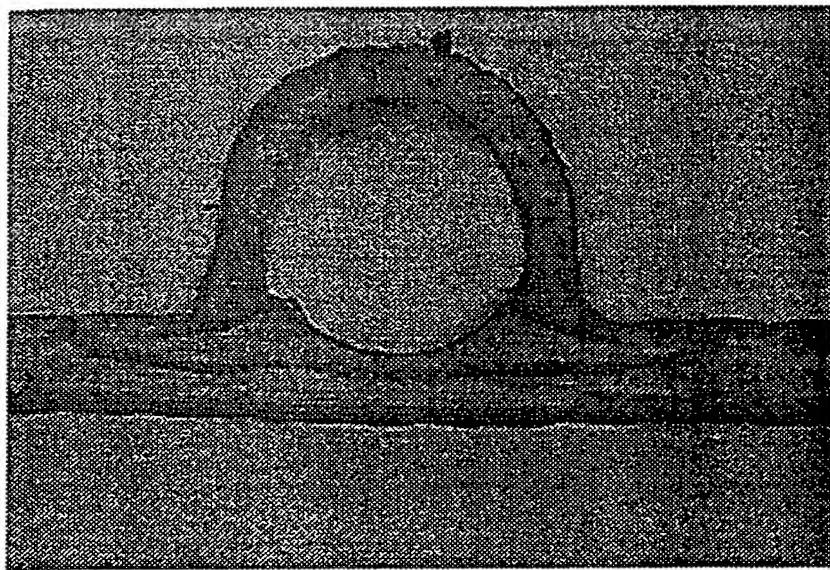
10/04/88

WO 01/12329

PCT/GB00/03142

6/6

Figure 8





21874

PATENT TRADEMARK OFFICE

**Dike, Bronstein, Roberts & Cushman  
Intellectual Property Practice Group  
EDWARDS & ANGELL, LLP  
P. O. Box 9169  
Boston, Massachusetts 02209**

Docket No. 71745/56925

# 5

**Declaration and Power of Attorney for Patent Application  
English Language Declaration**

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**"SAMPLING/DISPENSING DEVICE WITH PLUNGER AND HOUSING SET ONTO PLUNGER"**

the specification of which

(check one)

the specification attached hereto.

the specification in U.S. Application Serial Number 10/049,488, filed on February 12, 2002.

the specification in PCT international application Number,

filed on \_\_\_\_\_; and was amended on \_\_\_\_\_.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s) Priority Not Claimed

PCT/GB00/03142 \_\_\_\_\_ August 15, 2000 \_\_\_\_\_ [ ]  
(Number) (Country) (Day/Month/Year Filed)

99306463.3 \_\_\_\_\_ EP \_\_\_\_\_ August 17, 1999 \_\_\_\_\_ [ ]  
(Number) (Country) (Day/Month/Year Filed)

\_\_\_\_\_ [ ]  
(Number) (Country) (Day/Month/Year Filed)  
I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

\_\_\_\_\_ (Application Serial No.) \_\_\_\_\_ (Filing Date)

I hereby claim the benefit under 35 U.S.C. Section 120 of the United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark office all information known to me to be material to patentability as defined in Title 37, C.F.C., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

\_\_\_\_\_ (Application Serial No.) \_\_\_\_\_ (Filing Date) \_\_\_\_\_ (Status)  
(patented, pending, abandoned)

\_\_\_\_\_ (Application Serial No.) \_\_\_\_\_ (Filing Date) \_\_\_\_\_ (Status)  
(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these

statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

**POWER OF ATTORNEY:** As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

David G. Conlin	Reg. No. 27,026	David A. Tucker	Reg. No. 27,840
George W. Neuner	Reg. No. 26,964	George W. Hartnell, III	Reg. No. 42,639
Linda M. Buckley	Reg. No. 31,003	John B. Alexander	Reg. No. 48,399
Peter F. Corless	Reg. No. 33,860	Steven M. Jensen	Reg. No. 42,693
Peter J. Manus	Reg. No. 26,766	Kathryn A. Piffat	Reg. No. 34,901
Cara Z. Lowen	Reg. No. 38,227	Richard J. Roos	Reg. No. 45,053
William J. Daley, Jr.	Reg. No. 35,487	T. Carter Pledger	Reg. No. 29,424
Christine C. O'Day	Reg. No. 38,256	Peter J. Manso	Reg. No. 32,264
Robert L. Buchanan	Reg. No. 40,927	Dianne M. Rees	Reg. No. 45,281
Lisa S. Hazzard	Reg. No. 44,368	Edward J. Adamson	Reg. No. 50,927
Jack Penny	Reg. No. 36,984		

Send Correspondence to:

David G. Conlin, Esq.  
Dike, Bronstein, Roberts & Cushman  
Intellectual Property Practice Group of  
EDWARDS & ANGELL, LLP  
P.O. Box 9169  
Boston, Massachusetts 02209  
U.S.A.

Direct Telephone Calls to:  
*(name and telephone number)*

David G. Conlin  
Telephone: (617) 439-4444  
Facsimile: (617) 439-4170

<b>Full name of sole or first inventor</b> Thomas Richard Kerby EDWARDS	
<b>Sole or first inventor's signature</b> 	
<b>Date:</b> 17/05/02	
<b>Residence</b> United Kingdom	
<b>Citizenship</b> British	
<b>Post Office Address</b> 7 Leys Walk, Hauxton, Cambridge CB2 5HZ, UNITED KINGDOM GBX	

2 - 00

<b>Full name of second inventor, if any</b>	
John CASSELLS	JOHN MACLAREN CASSELLS
<b>Second inventor's signature</b>	<i>John M. Cassells</i>
<b>Date:</b>	27.6.02
<b>Residence</b>	
United Kingdom	
<b>Citizenship</b>	
British	
<b>Post Office Address</b>	
c/o The Technology Partnership plc, <u>Melbourn Science Park</u> , Cambridge Road, Melbourn, GBx Royston Herts SG8 6EE, UNITED KINGDOM	

3 - 00

<b>Full name of third inventor, if any</b>	
Nicholas Ian MOUNTENEY	NICHOLAS IAN MOUNTENEY
<b>Third inventor's signature</b>	<i>N. M. M.</i>
<b>Date:</b>	27/6/02
<b>Residence</b>	
United Kingdom	
<b>Citizenship</b>	
British	
<b>Post Office Address</b>	
30A Owl Way, <u>Hartford</u> , Huntingdon, Cambridgeshire, UNITED KINGDOM GBx	

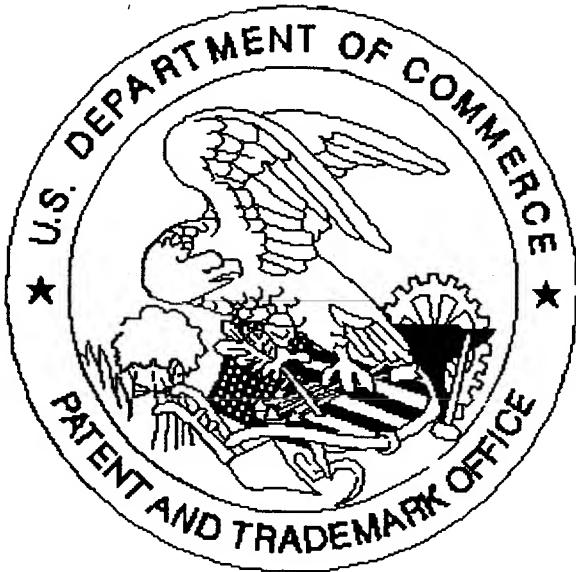
4 - 00

<b>Full name of fourth inventor, if any</b>	
Gerald AVISON	
<b>Fourth inventor's signature</b>	<i>G. Avison</i>
<b>Date:</b>	17/5/02
<b>Residence</b>	
United Kingdom	
<b>Citizenship</b>	
British	
<b>Post Office Address</b>	
59 Victoria Park, <u>Cambridge</u> , CB4 3EJ, UNITED KINGDOM GBx	

BOS2\_189561.1

SCANNED, # 8

United States Patent & Trademark Office  
Office of Initial Patent Examination -- Scanning Division



Application deficiencies found during scanning:

Page(s) \_\_\_\_\_ of \_\_\_\_\_ were not present  
for scanning. (Document title)

Page(s) \_\_\_\_\_ of \_\_\_\_\_ were not present  
for scanning. (Document title)

X *Scanned copy is best available. Page 6 of 6 of*  
*drawing is dark.*